Nonopioid Analgesics
Antidepressants, Adjuvant Therapies, and Muscle Relaxants

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Developed by: Chris Herndon, PharmD, CPE
Disclosures

- Nothing to disclose
Learning Objectives

- Describe where adjuvant analgesics act in the pain pathways
- State which adjuvants are considered first-line analgesics
- Choose an adjuvant analgesic for a given patient, based on current guidelines and/or evidence-based medicine
- Compare risks and benefits of different adjuvant analgesics for a given patient
**Pharmacotherapy** (based on a new taxonomy)

<table>
<thead>
<tr>
<th>Drug Class / Mechanism of action</th>
<th>IASP Pharmacology of Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>Antinociceptive</td>
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<tr>
<td>Anticonvulsants</td>
<td>Peripheral desensitization</td>
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<tr>
<td>TCAs</td>
<td>Descending modulator</td>
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<td>SNRIs</td>
<td>Descending modulator</td>
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<tr>
<td>Local anesthetics</td>
<td>Peripheral desensitization</td>
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<tr>
<td>NSAIDs</td>
<td>Antinociceptive</td>
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<td>Acetaminophen</td>
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<td>NMDA antagonists</td>
<td>Antihyperalgesic</td>
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<tr>
<td>Capsaicin</td>
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<td>Cannabinoids</td>
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<td>Corticosteroids</td>
<td>Peripheral desensitization</td>
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<tr>
<td>Skeletal muscle relaxants</td>
<td>Descending modulator</td>
</tr>
</tbody>
</table>

Where Do Adjuvants Work?
Adjuvants and Co-Analgesics

- Acetaminophen
- NSAIDs
- Antidepressants
- Anticonvulsants
- Anesthetics
- Skeletal muscle relaxants
- Antipsychotics
- Other
- Antidepressants
- Anticonvulsants
- Anesthetics
- Skeletal muscle relaxants
# Anticonvulsants

(available in US, excluding benzodiazepines)

<table>
<thead>
<tr>
<th>1st Generation Anticonvulsants</th>
<th>2nd / 3rd Generation Anticonvulsants</th>
</tr>
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<tbody>
<tr>
<td>Carbamazepine (Tegretol, others)</td>
<td>Eslicarbazepine (Aptiom)</td>
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<tr>
<td>Ethosuximide (Zarontin)</td>
<td>Ezogabine (Potiga)</td>
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<td>Pregabalin (Lyrica)</td>
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## Mechanism of Action
### 1st Generation Anticonvulsants

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## Mechanism of Action
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# Utility in Pain

## 1st Generation Anticonvulsants

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</table>

Results compiled from Medline and ClinicalTrials.gov (queried July 9, 2014)

Animal data may include models of hyperalgesia, musculoskeletal, or neuropathy

Level IV/V data = case reports or series

Level III = quasi experimental studies

Level II = randomized controlled trials
## Utility in Pain

### 2nd / 3rd Generation Anticonvulsants

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<tr>
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<td>Vigabatrin</td>
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</table>
Anticonvulsants—Suicidality

- Controversial
- FDA analysis of data from 199 clinical trials of 11 anticonvulsants
- Risk of suicidal thoughts or behaviors approximately doubles
- May present as early as 1 week following initiation
- Drug vs epilepsy?

Anticonvulsants—Dermatologic

- Stevens-Johnson Syndrome (SJS)
  - Sloughing in < 10% of body surface area
  - Mucous membranes affected in > 90%

- Toxic epidermal necrolysis (TEN)
  - Sloughing in > 30% of body surface area
  - Mucous membranes almost always affected

- Drug rash with eosinophilia and systemic symptoms (DRESS)
  - Also called drug induced hypersensitivity syndrome (DiHS)

Anticonvulsants—Dermatologic (cont’d)

- 90% of cases occur within first 60 days
- Carbamazepine / oxcarbazepine? / phenytoin / zonisamide
  - HLA B*1502 monitoring recommended (Asian ancestry)
  - Do not rechallenge with aromatic anticonvulsants
- Lamotrigine
  - Higher risk in children
  - Assoc. with titration

Anticonvulsants—Bone Disease

- Enzyme inducing vs non-enzyme inducing
  - Enzyme inducing
    - Increased catabolism of vitamin D and increased PTH
  - Non-enzyme inducing
    - Intestinal calcium absorption inhibition (direct)
    - Osteoclastic bone resorption stimulation (direct)

Anticonvulsants—Bone Disease (cont’d)

- Risk of fracture
  - Epilepsy vs control (RR 2.2; 95% CI 1.9-2.50)
  - Anticonvulsant vs no anticonvulsant (RR 2.64; 95% CI 1.82-3.82)
- Does fracture risk increase in non-epileptic use of anticonvulsants?
- General risk factors
  - Female, post-menopausal, Caucasian & Asian, old age, tobacco use, low BMI, low Ca and vit D intake
- AED related risk factors
  - High dose, multiple drug regimens, duration of therapy, chronic illnesses, metabolic acidosis, concomitant enzyme inducers
- Monitoring
  - National Osteoporosis Foundation recommendations unclear
  - Some recommend BMD testing (> 5 years duration of enzyme inducers and valproate)
  - Routine calcium, phosphate, and 25-OHD levels

References:
Anticonvulsants—Neurocognitive

- Psychomotor reaction time
- Learning, memory, and executive function
- Word finding

Considerable variance based on:
  - Age
  - Multiple anticonvulsants
  - Serum drug concentrations

All anticonvulsants appear to have some effect on neuropsych batteries

Lidocaine

- Topical anesthetic and Class 1b anti-arrhythmic
- Sodium channel blockade Na(v) 1.7
- Inhibition of acid sensing ion channels (ASIC)
- Available via OTC (0.5-4%) and prescription (5%)
- Lidocaine 5% patch applied directly to area of PHN
  - No more than 3 patches concurrently
  - 12 hours on, 12 hours off
- Infusion targeted to 5 mg/L

Antidepressants

**SNRI**
- Venlafaxine (Effexor)
- Desvenlafaxine (Pristiq)
- Duloxetine (Cymbalta)
- Milnacipran (Savella)
- Levomilnacipran (Fetzima)

**Atypicals**
- Bupropion (Wellbutrin, others)
- Mirtazapine (Remeron)
- Trazodone (Desryel)
- Vilazodone (Viibryd)

**TCA (tertiary vs secondary)**
- Doxepin
- Imipramine
- Amitriptyline
- Clomipramine
- Protriptyline
- Nortriptyline
- Desipramine

**In order of H1-Ki**

**SSRIs?**
- Paroxetine (Paxil)
- Escitalopram (Lexapro)
Tricyclic Antidepressants (TCAs)

<table>
<thead>
<tr>
<th>Tertiary amines</th>
<th>Secondary amines (NE&gt;5HT)</th>
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</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Nortriptyline</td>
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<tr>
<td>Imipramine</td>
<td>Desipramine</td>
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<tr>
<td>Clomipramine</td>
<td>Protriptyline</td>
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<tr>
<td>Doxepin</td>
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<tr>
<td>Trimipramine</td>
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</table>

- Secondary amines *tolerated* better than tertiary amines
- Secondary amines *equally* effective in pain as tertiary amines
- Therapeutic drug monitoring of questionable utility

TCAs—Cardiovascular Risk

- Orthostatic / postural hypotension
  - Alpha adrenergic blockade (even at low doses)
- Slowed cardiac conduction, tachycardia, ventricular fibrillation, heart block, and ventricular premature complexes (similar to Class Ia AA)
- Sudden cardiac death (unclear association with QTc prolongation)
  - Avoid doses > 100 mg / day amitriptyline equivalents
- Avoid in those with cardiovascular disease or established conduction abnormalities
- Unclear increase in risk in those without pre-existing disease
- Screen for known heart disease, syncope, palpitations, dyspnea, or chest pain
- Baseline ECG recommended by some in those > 40 years of age (> 50 years of age based on APA Depression Guidelines)
- Routine ECG monitoring not recommended unless CV symptoms arise

TCAs—Anticholinergic & Sedation

- **Muscarinic Ach receptor antagonists**
  - Blurred vision, constipation, dry mouth, urine retention, constipation, tachycardia, confusion, delirium, increased ocular pressure
  - Secondary amines < tertiary amines

- **Antihistaminergic effects (sedation, delirium)**
  - Maprotiline, amitriptyline, doxepin, and trimipramine
TCAs—Behavioral Health Risks

- **Abrupt discontinuation**
  - Withdrawal symptoms (GI, malaise, chills, rhinitis, and myalgias)
  - Rebound depression

- **Increased suicidality vs overdose toxicity**
  - Boxed warning for children, adolescents, young adults (18-24 years of age)
  - Cardiac (QTc) and anticholinergic toxicity at doses as little as 10x prescribed

- **Risk of “switching” to mania but small**

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## SSRI / SNRI / Atypical

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<tr>
<th>Selective Serotonin Reuptake Inhibitors</th>
<th>Serotonin Norepinephrine Reuptake Inhibitors</th>
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<tbody>
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<td>Fluoxetine</td>
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<td>Escitalopram*</td>
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*Small RCT data to support use in either chronic musculoskeletal or neuropathic pain

Serotonin Syndrome

- Mental status changes
  - Anxiety, agitated delirium, restlessness, disorientation
- Autonomic hyperactivity
  - Diaphoresis, tachycardia, hyperthermia, HTN, vomiting, and diarrhea
- Neuromuscular changes
  - Tremor, muscle rigidity, myoclonus, hyperreflexia, and clonus
- Severity may range from benign to lethal
- Solely a clinical diagnosis
- Patient and caregiver education paramount
- Consider serotonin active herbal / OTC products!!!
Diagnosis of SS—Hunter Criteria

- Serotonergic agent PLUS one of the following:
  - Spontaneous clonus
  - Inducible clonus and agitation or diaphoresis
  - Ocular clonus and agitation or diaphoresis
  - Tremor and hyperreflexia
  - Hypertonia
  - Temp above 38°C (100.4°F)

- Although clinical dx, consider CBC, BMP, INR, CPK, LFTs, UA, chest X-ray, head CT, to rule out differentials

SSRI / SNRI—Hyponatremia

- Incidence as high as 32% of those exposed
- Frequently seen within first 2 weeks of initiation
- SIADH-mediated

- Signs / symptoms
  - Fluid status related:
    - History of fluid loss, decreased skin turgor, orthostatic or persistent hypotension
  - CNS status related:
    - Weakness, lethargy, headache, anorexia (these are also symptoms of worsening depression and common side effects of the drugs)

- Monitoring recommendations vary and are opinion-based
  - Consider sodium monitoring within 1st month for those at risk
    - Diuretics, female gender, older age, low BMI, CYP3A4 interactions, and mild hyperkalemia upon initiation

SSRI / SNRI—Suicidality

- Warnings
- Effected populations
- Timing of risk
- Monitoring and followup

SSRI / SNRI—Cardiac Conduction

- Previously not associated with QTc prolongation or Torsades de Pointes
- Citalopram > escitalopram
- Dose limits
  - Citalopram 40 mg adults, 20 mg ≥ 65 years
  - Escitalopram 20 mg adults, 10 mg ≥ 65 years
- Consider baseline ECG in those with cardiac disease history

SSRI / SNRI Bleeding Risk

- Blocked serotonin uptake into platelet
- De-amplification of platelet aggregation
- Controversial data suggests:
  - Minimal risk of upper GI bleed as monotherapy
  - Increased risk of upper GI bleed in combination with NSAIDs
  - Acid suppression therapy decreases risk

Muscle Relaxants

- Antispasmodics
  - Cyclobenzaprine
  - Metaxalone
  - Methocarbamol
  - Orphenadrine citrate
  - Carisoprodol

- Antispasticity agents
  - Tizanidine
  - Baclofen
  - Diazepam
  - Dantrolene

- All equally effective for short-term relief of low back pain
- Not more effective than NSAIDs for acute low back pain
- Not recommended for chronic pain

III. Centrally-acting agents (spasmolytic drugs)

Muscle Relaxants (cont’d)

Mechanism
The stretch reflex:
1. muscle spindle
2. Ia afferents
3. efferents (motor neurons)
4. contraction
- CNS-acting drugs inhibit stretch reflex

Descending inhibitory neurons (not shown):
1. Inhibit alpha motor neurons
- CNS-acting drugs activate descending inhibitory pathways
Muscle Relaxants (cont’d)

Baclofen
- GABA analogue
- Selective GABA-B receptor agonist (↑ K+ conductance, ↓ Ca++ conductance)
- Muscle relaxant and analgesic (reduced substance P)
- Adverse effects: somnolence, increased seizure activity

Tizanidine
- Agonist of α2 receptors (presynaptic)
- Reduces adrenergic input to alpha motor neurons
- No effect on spinal cord reflex
- Less antihypertensive effect than clonidine
- Side effects: hypotension, asthenia
- BA-B receptor and effects:
Skeletal Muscle Relaxants

- Cyclobenzaprine—sedation, structurally a TCA
- Tizanidine—sedating, hypotension, best data
- Methocarbamol—less sedating, limiting evidence
- Orphenadrine—sedating, sodium channel blockade
- Carisoprodol—sedating, high abuse potential
- Diazepam—sedating, high abuse potential
- Metaxalone—less sedating, expensive
- Baclofen—data primarily intrathecal
- Dantrolene—hepatotoxicity
NMDA Receptor Antagonists

- Dextromethorphan
- Ketamine
- Methadone
- Memantine
- Amantadine
- Felbamate
- Levorphanol
NMDA Receptor Antagonists (cont’d)

- Mostly used for possible opioid-sparing effects
- Ketamine useful for acute post-op pain
- Several studies for chronic pain,
  very few positive results for ketamine
- Adverse effects are dose-limiting
- Potential for abuse
Conclusions

- Adjuvant and co-analgesics require judicious monitoring for safe use
- Extensive patient education regarding potential adverse effects is paramount
- Co-morbid disease processes and concurrent medications may obscure adverse effects